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(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING A BILE SALT AND A BUFFER FOR INCREASED BIOAVAILABILITY OF AN ACTIVE COMPOUND

(57) Abstract

Compositions containing a bile salt and a buffer such as a carbonate or bicarbonate salt which is adapted to buffer the gut to a pH of from 7.5 to 9 are capable of increasing the bioavailability of an active molecule whilst minimising the toxic side effects which are generally associated with bile salts.

When a bile salt is used in the compositions of the present invention, it is preferred that there is a soluble counter-ion present such as sodium or potassium. It is also possible to use, for example, an ammonium ion but this is less preferred.

Bile salts are naturally occurring surfactants. They are a group of compounds with a common "backbone" structure based on cholanic acid found in all mammals and higher vegetables. Bile salts may be mono-, di- or tri-hydroxylated; they always contain a 3α-hydroxyl group whereas the other hydroxyl groups, most commonly found at C_6, C_7 or C_{12}, may be positioned either above (β) or below (α) the plane of the molecule.

Within the class of compounds described as bile salts are included amphiphilic polyhydric sterols bearing carboxyl groups as part of the primary side chain. The most common examples of these in mammals result from cholesterol metabolism and are found in the bile and, in derivatised form, throughout the intestine.

In the context of this specification, the term may also apply to synthetic analogues of naturally occurring bile salts which display similar biological effects, or to microbially derived molecules such as fusidic acid and its derivatives.

The bile salt may be either unconjugated or conjugated. The term "unconjugated" refers to a bile salt in which the primary side chain has a single carboxyl group which is at the terminal position and which is unsubstituted. Examples of unconjugated bile salts include cholate, ursodeoxycholate, chenodeoxycholate and deoxycholate. A

conjugated bile salt is one in which the primary side chain has a carboxyl group which is substituted. Often the substituent will be an amino acid derivative which is linked via its nitrogen atom to the carboxyl group of the bile salt. Examples of conjugated bile salts include taurocholate, glycocholate, taurodeoxycholate and glycodeoxycholate.

The quantity of bile acid contained in a single dose of the formulation will vary depending on the particular bile acid chosen and the rate and extent to which that bile acid dissolves in the aqueous fluid contained in the intestine. For chenodeoxycholic acid, and most other bile acids, this is likely to be within the range 10 mg to 1 g, preferably between 20 mg to 200 mg, and most preferably 30 mg to 100 mg. For deoxycholic acid, the maximum will generally not exceed 500 mg, in view of its slightly greater activity.

The gut of many animals (particularly humans and other mammals) is naturally buffered to a pH below neutrality. Compositions of the invention comprise an agent adapted to adjust the pH of the gut to a pH of from 7.5 to 9. The agent is "adapted" to adjust the pH either by its chemical nature or by the amount in which it is present or, usually, both. The optimum pH to which the gut is adjusted is in the range 7.8 to 8.3.

While simple agents adapted to adjust the pH of the gut into the range specified above may be successfully used in the invention, it is preferred that the pH adjusting agent also has the capability of buffering the gut to a pH within the stated range. This can give a more long lasting effect, which may be desired in many